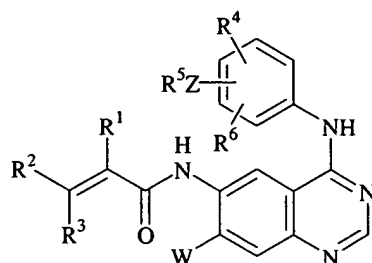


WHAT IS CLAIMED IS:

1. A method of making a compound of Formula 1,



1

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof, in which

R^1 , R^2 and R^3 are independently hydrogen, halogen, NO_2 , CN, CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} heterocyclyl, carboxy, C_{1-6} alkoxy, C_{1-6} alkylcarbamoyl, aryl- $(\text{CH}_2)_m$, heteroaryl- $(\text{CH}_2)_m$, heterocyclyl- $(\text{CH}_2)_m$, $(\text{CH}_2)_m\text{CO}_2\text{R}^8$, $(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^8$, $(\text{CH}_2)_m\text{SO}_2\text{NR}^8\text{R}^9$, OR^8 , SR^8 , $(\text{CH}_2)_m\text{NR}^8\text{R}^9$, $(\text{CH}_2)_m\text{N}(\text{O})\text{R}^8\text{R}^9$, $(\text{CH}_2)_m\text{P}(\text{O})(\text{OR}^8)(\text{OR}^9)$, $(\text{CH}_2)_m\text{COR}^8$, $(\text{CH}_2)_m\text{CO}_2\text{R}^8$, $(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{R}^9$, $(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{SO}_2\text{R}^8$, $(\text{CH}_2)_m\text{NR}^8\text{SO}_2\text{R}^9$, $(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{OR}^9$, $(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^8$, or $(\text{CH}_2)_m\text{SO}_2\text{NR}^8\text{R}^9$, wherein aryl- $(\text{CH}_2)_m$ includes phenylalkyl or substituted phenylalkyl having from one to three substituents that are independently NO_2 , CN, CF_3 , C_{1-6} alkyl-NH, $(\text{C}_{1-6}$ alkyl) $_2\text{N}$, or monocyclic heteroaryl, and each C_{1-6} alkyl is optionally substituted with OH, NH_2 or -N(A)B;

R^4 and R^6 are independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, C_{1-4} alkyldiamino, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, dicarbamoyl, carbamyl, C_{1-4} alkoxy, cyano, nitro, or trifluoromethyl;

R^5 is phenyl, pyridyl, furyl, thiazolyl, imidazolyl or thienyl, each optionally having one or two substituents that are independently halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, cyano, C_{1-6} alkyl-NH or $(\text{C}_{1-6}$ alkyl) $_2\text{N}$;

W is SR^7 , OR^7 or NHR^7 ; and

Z is hydrogen, halogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkoxy, C₃₋₈ cycloalkoxy, nitro, C₁₋₆ haloalkyl, hydroxy, C₁₋₆ acyloxy, NH₂, C₁₋₆ alkyl-NH, (C₁₋₆ alkyl)₂N, C₃₋₈ cycloalkyl-NH, (C₃₋₈ cycloalkyl)₂N, hydroxymethyl, C₁₋₆ alkylcarbonyl, cyano, azido, C₁₋₆ thioalkyl, C₁₋₆ sulfinylalkyl, C₁₋₆ sulfonylalkyl, C₃₋₈ thiocycloalkyl, C₃₋₈ sulfinylcycloalkyl, C₃₋₈ sulfonylcycloalkyl, mercapto, C₁₋₆ alkoxycarbonyl, C₃₋₈ cycloalkoxycarbonyl, C₂₋₄ alkenyl, C₄₋₈ cycloalkenyl, or C₂₋₄ alkynyl, provided that when Z is monovalent, R⁵ is absent;

wherein, R⁷ is hydrogen, C₁₋₆ alkyl, piperidin-1-yl-(CH₂)_m, piperazin-1-yl-(CH₂)_m, 4-C₁₋₆ alkyl-piperazin-1-yl-(CH₂)_m, pyrrolidin-1-yl-(CH₂)_m, pyridinyl-(CH₂)_m, imidazolyl-(CH₂)_m, imidazol-1-yl-(CH₂)_m, morpholin-4-yl-(CH₂)_m, thiomorpholin-4-yl-(CH₂)_m, or hexahydroazepin-1-yl-(CH₂)_m, wherein each C₁₋₆ alkyl optionally includes one or more substituents that are OH, NH₂ or -N(A)B;

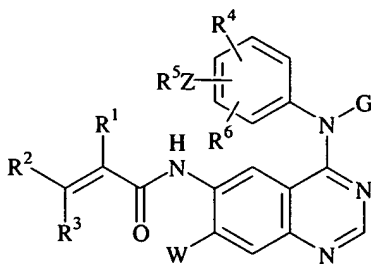
R⁸ and R⁹ are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, arylalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or heteroarylalkyl;

A and B are independently hydrogen, C₁₋₆ alkyl, (CH₂)_mOH, piperidin-1-yl-(CH₂)_m, piperazin-1-yl-(CH₂)_m, 4-C₁₋₆ alkyl-piperazin-1-yl-(CH₂)_m, pyrrolidin-1-yl-(CH₂)_m, pyridinyl-(CH₂)_m, imidazolyl-(CH₂)_m, or imidazol-1-yl-(CH₂)_m; and

n and m are, respectively, integers from zero to two, inclusive, and from zero to four, inclusive;

the method comprising:

removing a protecting group, G, from a compound of Formula 10,

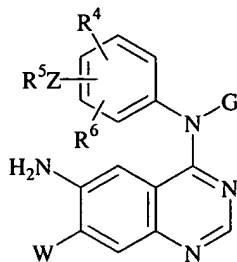


10

to yield the compound of Formula 1; and

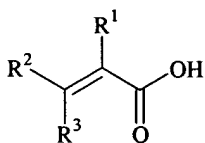
optionally converting the compound of Formula 1 to a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

2. The method of claim 1, further comprising reacting a compound of Formula 7,



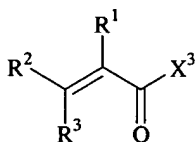
7

with a compound of Formula 8,



8

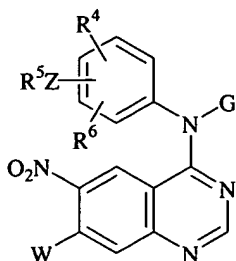
or with a compound of Formula 9,



9

to yield the compound of Formula 10, wherein G, R¹, R², R³, R⁴, R⁵, R⁶, W, and Z are as defined in claim 1, X³ is a leaving group, and provided that when G is Boc, W is not alkoxy.

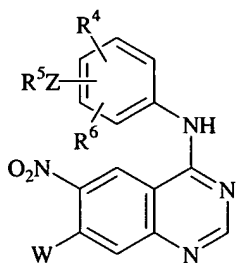
3. The method of claim 2, further comprising reacting a compound of Formula 6,



6

with hydrogen in the presence of a catalyst or with a reducing agent to yield the compound of claim 7, wherein G, R⁴, R⁵, R⁶, W, and Z are as defined in claim 1.

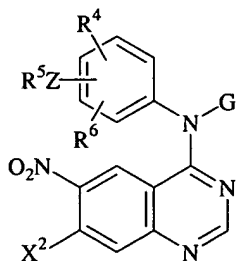
4. The method of claim 3, further comprising installing the protecting group, G, on a compound of Formula 5,



5

to yield the compound of Formula 6, wherein G, R⁴, R⁵, R⁶, W, and Z are as defined in claim 1.

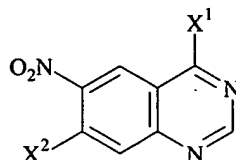
5. The method of claim 3, further comprising displacing a leaving group, X², of Formula 12,



12

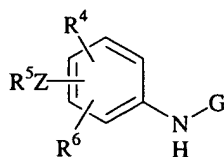
with W to yield the compound of Formula 6, wherein G, R⁴, R⁵, R⁶, W, and Z are as defined in claim 1, and provided that when G is Boc, X² is not halogen.

6. The method of claim 5, further comprising reacting a compound of Formula 2,



2

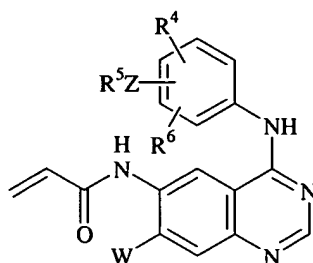
with a compound of Formula 11,



11

to yield the compound of Formula 12, wherein G, R⁴, R⁵, R⁶, and Z are as defined in claim 1, X² is as defined in claim 5, and X¹ is a leaving group.

7. The method of claim 1, wherein G is acetyl.
8. The method of claim 1, wherein G is dimethoxy benzyl.
9. The method of claim 1, wherein R¹, R², R³ and Z are each hydrogen, and R⁴ and R⁶ are each halogen.
10. The method of claim 1, wherein W is morpholin-4-yl-alkoxy.
11. The method of claim 1, wherein the compound of Formula 1 is *N*-[4-(3-chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide.
12. A method of making a compound of Formula 23,



23

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, in which

R^4 and R^6 are independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy,

C_{1-4} alkylamino, C_{1-4} alkylidiamino, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl,

C_{1-4} alkylsulfonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, dicarbamoyl,

carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro, or trifluoromethyl;

R^5 is phenyl, pyridyl, furyl, thiazolyl, imidazolyl or thienyl, each optionally having one or two substituents that are independently halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, cyano, C_{1-6} alkyl-NH or $(C_{1-6} \text{ alkyl})_2N$;

W is SR^7 , OR^7 or NHR^7 ; and

Z is hydrogen, halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{3-8} cycloalkoxy, nitro, C_{1-6} haloalkyl, hydroxy, C_{1-6} acyloxy, NH_2 , C_{1-6} alkyl-NH, $(C_{1-6} \text{ alkyl})_2N$, C_{3-8} cycloalkyl-NH, $(C_{3-8} \text{ cycloalkyl})_2N$, hydroxymethyl, C_{1-6} alkylcarbonyl, cyano, azido, C_{1-6} thioalkyl, C_{1-6} sulfinylalkyl, C_{1-6} sulfonylalkyl, C_{3-8} thiocycloalkyl, C_{3-8} sulfinylcycloalkyl, C_{3-8} sulfonylcycloalkyl, mercapto, C_{1-6} alkoxycarbonyl, C_{3-8} cycloalkoxycarbonyl, C_{2-4} alkenyl, C_{4-8} cycloalkenyl, or C_{2-4} alkynyl, provided that when Z is monovalent, R^5 is absent;

wherein, R^7 is hydrogen, C_{1-6} alkyl, piperidin-1-yl- $(CH_2)_m$, piperazin-1-yl- $(CH_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(CH_2)_m$, pyrrolidin-1-yl- $(CH_2)_m$, pyridinyl- $(CH_2)_m$, imidazolyl- $(CH_2)_m$, imidazol-1-yl- $(CH_2)_m$, morpholin-4-yl- $(CH_2)_m$, thiomorpholin-4-yl- $(CH_2)_m$, or hexahydroazepin-1-yl- $(CH_2)_m$, wherein each C_{1-6} alkyl optionally includes one or more substituents that are OH, NH_2 or $-N(A)B$;

A and B are independently hydrogen, C_{1-6} alkyl, $(CH_2)_mOH$, piperidin-1-yl- $(CH_2)_m$, piperazin-1-yl- $(CH_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(CH_2)_m$, pyrrolidin-1-

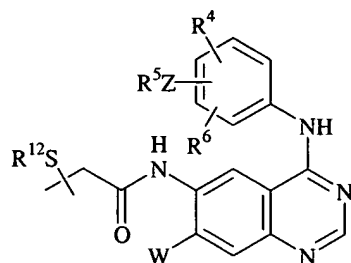
yl-(CH₂)_m, pyridinyl-(CH₂)_m, imidazolyl-(CH₂)_m, or imidazol-1-yl-(CH₂)_m;

and

m is an integer from zero to four, inclusive;

the method comprising:

eliminating SR¹² from a compound of Formula 22,

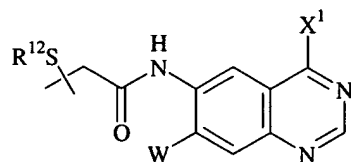


22

to yield the compound of Formula 23; and

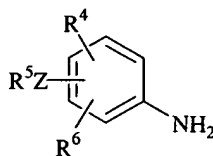
optionally converting the compound of Formula 23 to a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, wherein R¹² is C₁₋₆ alkyl or aryl.

13. The method of claim 12, further comprising reacting a compound of Formula 21,



21

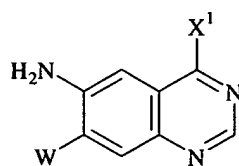
with a compound of Formula 3,



3

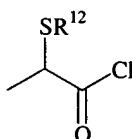
to yield the compound of Formula 22, wherein R⁴, R⁵, R⁶, R¹², W, and Z are as defined in claim 12, and X¹ is a leaving group.

14. The method of claim 13, further comprising reacting a compound of Formula 18,



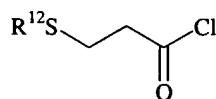
18

with a compound of Formula 19,



19

or with a compound of Formula 20,



20

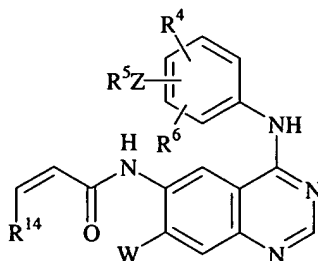
to yield the compound of Formula 21, wherein R^{12} and W are as defined in claim 12, and X^1 is as defined in claim 13.

15. The method of claim 12, wherein Z is hydrogen, and R^4 and R^6 are each halogen.

16. The method of claim 12, wherein W is morpholin-4-yl-alkoxy.

17. The method of claim 12, wherein the compound of Formula 23 is *N*-[4-(3-chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide.

18. A method of making a compound of Formula 29,



29

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, in which

R^4 and R^6 are independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy,

C_{1-4} alkylamino, C_{1-4} alkyldiamino, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl,

C_{1-4} alkylsulfonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyle, dicarbamoyle,

carbamyl, C_{1-4} alkoxycarbonyl, cyano, nitro, or trifluoromethyl;

R^5 is phenyl, pyridyl, furyl, thiazolyl, imidazolyl or thienyl, each optionally having one or two substituents that are independently halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, cyano, C_{1-6} alkyl-NH or $(C_{1-6} \text{ alkyl})_2N$;

W is SR^7 , OR^7 or NHR^7 ;

Z is hydrogen, halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{3-8} cycloalkoxy,

nitro, C_{1-6} haloalkyl, hydroxy, C_{1-6} acyloxy, NH_2 , C_{1-6} alkyl-NH,

$(C_{1-6} \text{ alkyl})_2N$, C_{3-8} cycloalkyl-NH, $(C_{3-8} \text{ cycloalkyl})_2N$, hydroxymethyl,

C_{1-6} alkylcarbonyl, cyano, azido, C_{1-6} thioalkyl, C_{1-6} sulfinylalkyl,

C_{1-6} sulfonylalkyl, C_{3-8} thiocycloalkyl, C_{3-8} sulfinylcycloalkyl,

C_{3-8} sulfonylcycloalkyl, mercapto, C_{1-6} alkoxycarbonyl,

C_{3-8} cycloalkoxycarbonyl, C_{2-4} alkenyl, C_{4-8} cycloalkenyl, or C_{2-4} alkynyl,

provided that when Z is monovalent, R^5 is absent; and

R^{14} is hydrogen, halogen, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{2-6} alkenyl or C_{2-6} alkynyl substituted with hydroxy, alkoxy, amino or alkylamino;

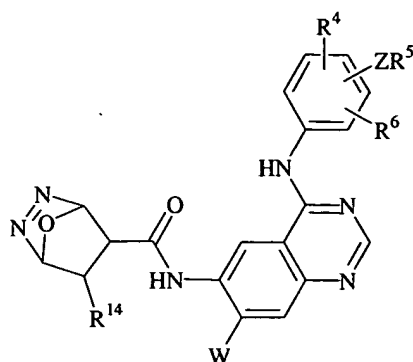
wherein, R^7 is hydrogen, C_{1-6} alkyl, piperidin-1-yl- $(CH_2)_m$, piperazin-1-yl- $(CH_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(CH_2)_m$, pyrrolidin-1-yl- $(CH_2)_m$, pyridinyl- $(CH_2)_m$, imidazolyl- $(CH_2)_m$, imidazol-1-yl- $(CH_2)_m$, morpholin-4-yl- $(CH_2)_m$, thiomorpholin-4-yl- $(CH_2)_m$, or hexahydroazepin-1-yl- $(CH_2)_m$, wherein each C_{1-6} alkyl optionally includes one or more substituents that are OH, NH_2 or -N(A)B;

A and B are independently hydrogen, C_{1-6} alkyl, $(CH_2)_mOH$, piperidin-1-yl- $(CH_2)_m$, piperazin-1-yl- $(CH_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(CH_2)_m$, pyrrolidin-1-yl- $(CH_2)_m$, pyridinyl- $(CH_2)_m$, imidazolyl- $(CH_2)_m$, or imidazol-1-yl- $(CH_2)_m$; and

m is an integer from zero to four, inclusive;

the method comprising:

removing [1,3,4]oxadiazole from a compound of Formula 28,

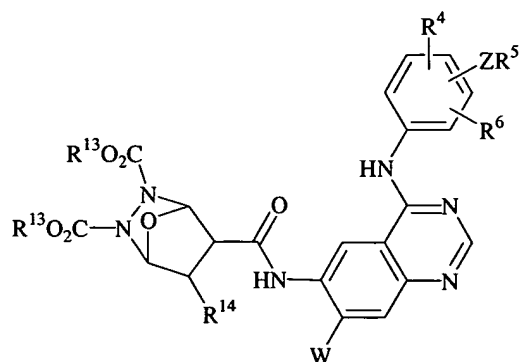


28

to yield the compound of Formula 29; and

optionally converting the compound of Formula 29 to a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

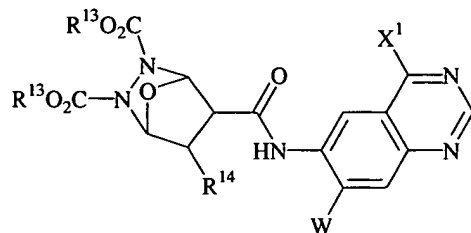
19. The method of claim 18, further comprising removing ester moieties, R¹³O₂C, from a compound of Formula 27,



27

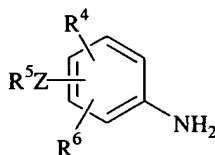
to yield the compound of Formula 28, wherein R⁴, R⁵, R⁶, R¹⁴, W, and Z are as defined in claim 18, and R¹³ is C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, TMS-(CH₂)_m or aryl-(CH₂)_m.

20. The method of claim 19, further comprising reacting a compound of Formula 26,



26

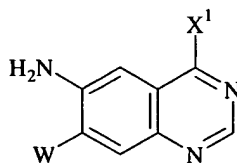
with a compound of Formula 3,



3

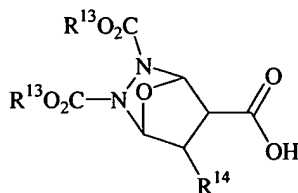
to yield the compound of Formula 27, wherein R^4 , R^5 , R^6 , R^{14} , W , and Z are as defined in claim 18, R^{13} is as defined in claim 19, and X^1 is a leaving group.

21. The method of claim 20, further comprising reacting a compound of Formula 18,



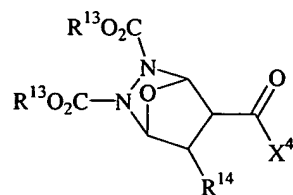
18

with a compound of Formula 24



24

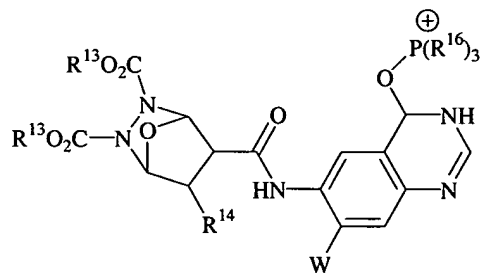
or with a compound of Formula 25



25

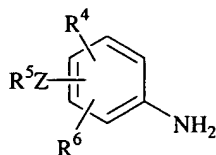
to yield the compound of Formula 26, wherein R^{14} and W are as defined in claim 18, R^{13} is as defined in claim 19, X^1 is as defined in claim 20, and X^4 is a leaving group.

22. The method of claim 19, further comprising reacting a compound of Formula 36,



36

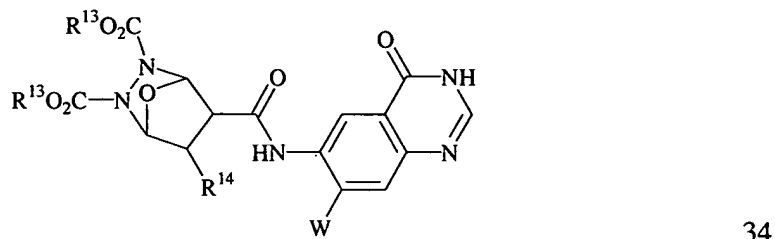
with a compound of Formula 3,



3

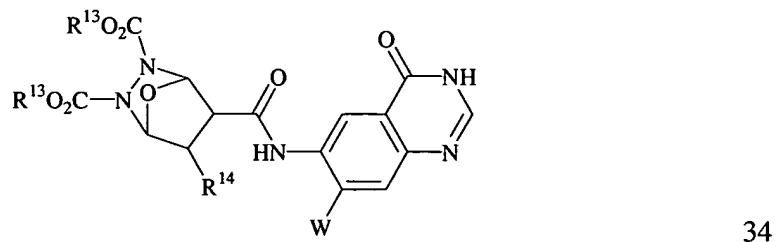
to yield the compound of Formula 27, wherein R^4 , R^5 , R^6 , R^{14} , W , and Z are as defined in claim 18, R^{13} is as defined in claim 19, and R^{16} is C_{1-6} alkyl, phenyl, or phenoxy.

23. The method of claim 22, further comprising reacting a compound of Formula 34



with $(R^{16})_3P(X^5)_2$ to yield the compound of 36, wherein R^{14} and W are as defined in claim 18, R^{13} is as defined in claim 19, R^{16} is as defined in claim 22, and X^5 is hydrogen, halogen or absent.

24. The method of claim 19, further comprising reacting a compound of Formula 34,

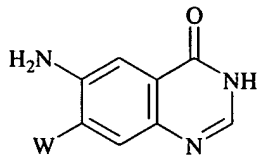


with a compound of Formula 37,



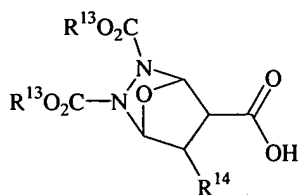
to yield the compound of Formula 27, wherein R^4 , R^5 , R^6 , R^{14} , W, and Z are as defined in claim 18, R^{13} is as defined in claim 19, and R^{17} is C_{1-6} alkyl, phenyl or phenoxy.

25. The method of claim 24, further comprising reacting a compound of Formula 33,



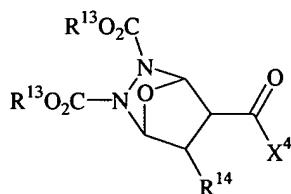
33

with a compound of Formula 24,



24

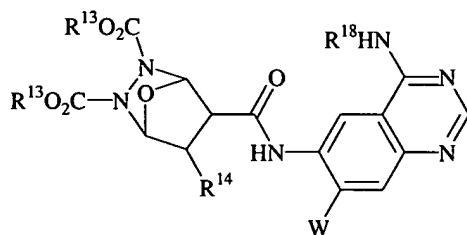
or with a compound of Formula 25,



25

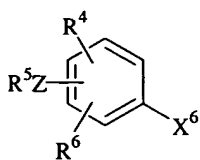
to yield the compound of Formula 34, wherein R^{14} and W are as defined in claim 18, R^{13} is as defined in claim 19, and X^4 is a leaving group.

26. The method of claim 19, further comprising reacting a compound of Formula 38,



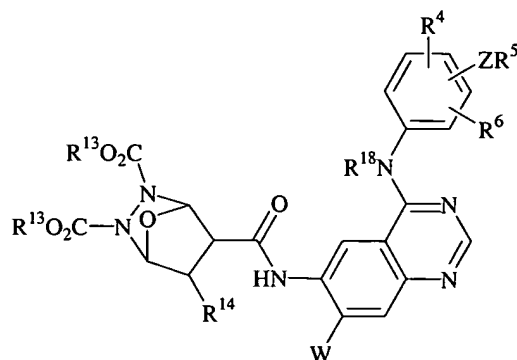
38

with a compound of Formula 39,



39

in the presence of a catalyst to yield a compound of Formula 40,



40

wherein R^4 , R^5 , R^6 , R^{14} , W , and Z are as defined in claim 18, R^{13} is as defined in claim 19, X^6 is halogen, and R^{18} is hydrogen or a group that facilitates coupling of the compounds of Formula 38 and Formula 39; and

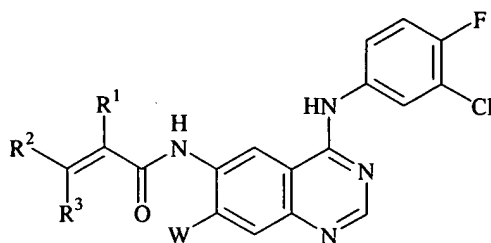
optionally reacting the compound of Formula 40 with an acid to yield the compound of Formula 27 when R^{18} is non-hydrogen.

27. The method of claim 18, wherein Z and R^{14} are each hydrogen, and R^4 and R^6 are each halogen.

28. The method of claim 18, wherein W is morpholin-4-yl-alkoxy.

29. The method of claim 18, wherein the compound of Formula 29 is *N*-[4-(3-chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide.

30. A method of making a compound of Formula 46,



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or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, in which

R^1 , R^2 and R^3 are independently hydrogen, halogen, NO_2 , CN , CF_3 , C_{1-6} alkyl, C_{1-6}

haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} heterocyclyl,

carboxy, C_{1-6} alkoxy carbonyl, C_{1-6} alkyl carbamoyl, aryl- $(\text{CH}_2)_m$,

heteroaryl- $(\text{CH}_2)_m$, heterocyclyl- $(\text{CH}_2)_m$, $(\text{CH}_2)_m\text{CO}_2\text{R}^8$, $(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^8$,

$(\text{CH}_2)_m\text{SO}_2\text{NR}^8\text{R}^9$, OR^8 , SR^8 , $(\text{CH}_2)_m\text{NR}^8\text{R}^9$, $(\text{CH}_2)_m\text{N}(\text{O})\text{R}^8\text{R}^9$,

$(\text{CH}_2)_m\text{P}(\text{O})(\text{OR}^8)(\text{OR}^9)$, $(\text{CH}_2)_m\text{COR}^8$, $(\text{CH}_2)_m\text{CO}_2\text{R}^8$, $(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{R}^9$,

$(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{SO}_2\text{R}^8$, $(\text{CH}_2)_m\text{NR}^8\text{SO}_2\text{R}^9$, $(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{OR}^9$,

$(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^8$, or $(\text{CH}_2)_m\text{SO}_2\text{NR}^8\text{R}^9$, wherein aryl- $(\text{CH}_2)_m$ includes

phenylalkyl or substituted phenylalkyl having from one to three substituents

that are independently NO_2 , CN , CF_3 , C_{1-6} alkyl-NH, $(\text{C}_{1-6}$ alkyl) $_2\text{N}$, or

monocyclic heteroaryl, and each C_{1-6} alkyl is optionally substituted with OH,

NH_2 or $-\text{N}(\text{A})\text{B}$; and

W is SR^7 , OR^7 or NHR^7 ;

wherein, R^7 is hydrogen, C_{1-6} alkyl, piperidin-1-yl- $(\text{CH}_2)_m$, piperazin-1-yl- $(\text{CH}_2)_m$, 4-

C_{1-6} alkyl-piperazin-1-yl- $(\text{CH}_2)_m$, pyrrolidin-1-yl- $(\text{CH}_2)_m$, pyridinyl- $(\text{CH}_2)_m$,

imidazolyl- $(\text{CH}_2)_m$, imidazol-1-yl- $(\text{CH}_2)_m$, morpholin-4-yl- $(\text{CH}_2)_m$, or

thiomorpholin-4-yl- $(\text{CH}_2)_m$, or hexahydroazepin-1-yl- $(\text{CH}_2)_m$, wherein each

C_{1-6} alkyl optionally includes one or more substituents that are OH, NH_2 or

$-\text{N}(\text{A})\text{B}$;

R^8 and R^9 are each independently hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl,

C_{2-6} alkynyl, arylalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or

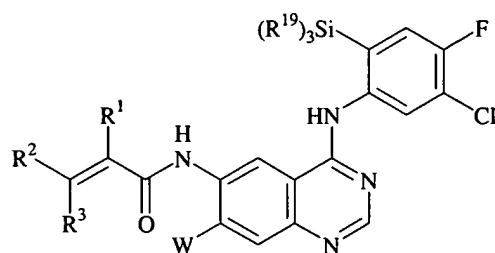
heteroarylalkyl;

A and B are independently hydrogen, C₁₋₆ alkyl, (CH₂)_mOH, piperidin-1-yl-(CH₂)_m, piperazin-1-yl-(CH₂)_m, 4-C₁₋₆ alkyl-piperazin-1-yl-(CH₂)_m, pyrrolidin-1-yl-(CH₂)_m, pyridinyl-(CH₂)_m, imidazolyl-(CH₂)_m, or imidazol-1-yl-(CH₂)_m; and

n and m are, respectively, integers from zero to two, inclusive, and from zero to four, inclusive;

the method comprising:

treating a compound of Formula 45,



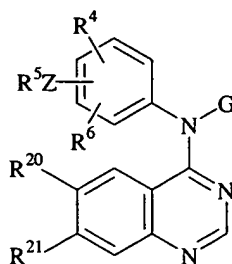
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with an acid to yield the compound of Formula 46, wherein R¹⁹ is C₁₋₄ alkyl, C₁₋₄ alkoxy or aryl; and

optionally converting the compound of Formula 46 to a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

31. The method of claim 30, wherein R¹, R² and R³ are each hydrogen.
32. The method of claim 30, wherein W is morpholin-4-yl-alkoxy.
33. The method of claim 30, wherein the compound of Formula 46 is *N*-[4-(3-chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide.

34. A compound of Formula 47,



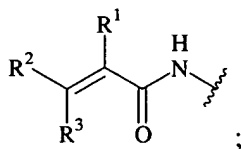
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or a pharmaceutically acceptable salt, ester, amide or prodrug thereof, in which

R^4 and R^6 are independently hydrogen, hydroxy, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, C_{1-4} alkyldiamino, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl, dicarbamoyl, carbamyl, C_{1-4} alkoxy carbonyl, cyano, nitro, or trifluoromethyl;

R^5 is phenyl, pyridyl, furyl, thiazolyl, imidazolyl or thienyl, each optionally having one or two substituents that are independently halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, cyano, C_{1-6} alkyl-NH or $(C_{1-6} \text{ alkyl})_2N$;

R^{20} is NH_2 , NO_2 , or



R^{21} is SR^7 , OR^7 , NHR^7 or a leaving group;

Z is hydrogen, halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{3-8} cycloalkoxy, nitro, C_{1-6} haloalkyl, hydroxy, C_{1-6} acyloxy, NH_2 , C_{1-6} alkyl-NH, $(C_{1-6} \text{ alkyl})_2N$, C_{3-8} cycloalkyl-NH, $(C_{3-8} \text{ cycloalkyl})_2N$, hydroxymethyl, C_{1-6} alkylcarbonyl, cyano, azido, C_{1-6} thioalkyl, C_{1-6} sulfinylalkyl, C_{1-6} sulfonylalkyl, C_{3-8} thiocycloalkyl, C_{3-8} sulfinylcycloalkyl, C_{3-8} sulfonylcycloalkyl, mercapto, C_{1-6} alkoxy carbonyl, C_{3-8} cycloalkoxy carbonyl, C_{2-4} alkenyl, C_{4-8} cycloalkenyl, or C_{2-4} alkynyl, provided that when Z is monovalent, R^5 is absent; and

G is a protecting group, provided that when G is Boc and R^{20} is NH_2 or NO_2 , R^{21} is not halogen or alkoxy;

wherein R^1 , R^2 and R^3 are independently hydrogen, halogen, NO_2 , CN, CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} heterocyclyl, carboxy, C_{1-6} alkoxy carbonyl, C_{1-6} alkyl carbamoyl, aryl- $(CH_2)_m$, heteroaryl- $(CH_2)_m$, heterocyclyl- $(CH_2)_m$, $(CH_2)_mCO_2R^8$, $(CH_2)_mS(O)_nR^8$, $(CH_2)_mSO_2NR^8R^9$, OR^8 , SR^8 , $(CH_2)_mNR^8R^9$, $(CH_2)_mN(O)R^8R^9$, $(CH_2)_mP(O)(OR^8)(OR^9)$, $(CH_2)_mCOR^8$, $(CH_2)_mCO_2R^8$, $(CH_2)_mC(O)NR^8R^9$, $(CH_2)_mC(O)NR^8SO_2R^8$, $(CH_2)_mNR^8SO_2R^9$, $(CH_2)_mC(O)NR^8OR^9$, $(CH_2)_mS(O)_nR^8$, or $(CH_2)_mSO_2NR^8R^9$, wherein aryl- $(CH_2)_m$ includes phenylalkyl or substituted phenylalkyl having from one to three substituents that are independently NO_2 , CN, CF_3 , C_{1-6} alkyl-NH, $(C_{1-6}$ alkyl) $_2N$, or monocyclic heteroaryl, and each C_{1-6} alkyl is optionally substituted with OH, NH_2 or $-N(A)B$;

R^7 is hydrogen, C_{1-6} alkyl, piperidin-1-yl- $(CH_2)_m$, piperazin-1-yl- $(CH_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(CH_2)_m$, pyrrolidin-1-yl- $(CH_2)_m$, pyridinyl- $(CH_2)_m$, imidazolyl- $(CH_2)_m$, imidazol-1-yl- $(CH_2)_m$, morpholin-4-yl- $(CH_2)_m$, thiomorpholin-4-yl- $(CH_2)_m$, or hexahydroazepin-1-yl- $(CH_2)_m$, wherein each C_{1-6} alkyl optionally includes one or more substituents that are OH, NH_2 or $-N(A)B$;

R^8 and R^9 are each independently hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, arylalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or heteroarylalkyl;

A and B are independently hydrogen, C_{1-6} alkyl, $(CH_2)_mOH$, piperidin-1-yl- $(CH_2)_m$, piperazin-1-yl- $(CH_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(CH_2)_m$, pyrrolidin-1-yl- $(CH_2)_m$, pyridinyl- $(CH_2)_m$, imidazolyl- $(CH_2)_m$, or imidazol-1-yl- $(CH_2)_m$; and

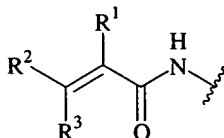
n and m are, respectively, integers from zero to two, inclusive, and from zero to four, inclusive.

35. The compound of claim 34, wherein G is acetyl.

36. The compound of claim 34, wherein G is dimethoxy benzyl.

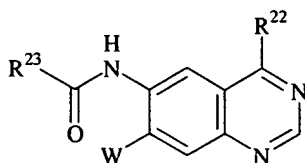
37. The compound of claim 34, wherein R^{20} is NH_2 .

38. The compound of claim 37, wherein R^{21} is SR^7 , OR^7 or NHR^7 .
39. The compound of claim 34, wherein R^{20} is NO_2 .
40. The compound of claim 39, wherein R^{21} is SR^7 , OR^7 or NHR^7 .
41. The compound of claim 34, wherein R^{20} is



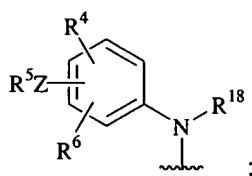
42. The compound of claim 41, wherein R^1 , R^2 , R^3 and Z are each hydrogen, and R^4 and R^6 are each halogen.
43. The compound of claim 34, wherein R^{21} is morpholin-4-yl-alkoxy.
44. A compound selected from:
(3-chloro-4-fluoro-phenyl)-(3,4-dimethoxy-benzyl)-(7-fluoro-6-nitro-quinazolin-4-yl)-amine;
(3-chloro-4-fluoro-phenyl)-(3,4-dimethoxy-benzyl)-[7-(3-morpholin-4-yl-propoxy)-6-nitro-quinazolin-4-yl]-amine;
*N*4-(3-chloro-4-fluoro-phenyl)-*N*4-(3,4-dimethoxy-benzyl)-7-(3-morpholin-4-yl-propoxy)-quinazoline-4,6-diamine;
N-[4-[(3-chloro-4-fluoro-phenyl)-(3,4-dimethoxy-benzyl)-amino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide;
N-(3-chloro-4-fluoro-phenyl)-*N*-[7-(3-morpholin-4-yl-propoxy)-6-nitro-quinazolin-4-yl]-acetamide;
N-[6-amino-7-(3-morpholin-4-yl-propoxy)-quinazolin-4-yl]-*N*-(3-chloro-4-fluoro-phenyl)-acetamide; and
N-[4-[acetyl-(3-chloro-4-fluoro-phenyl)-amino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide;
or a pharmaceutically acceptable salt thereof.

45. A compound of Formula 48,

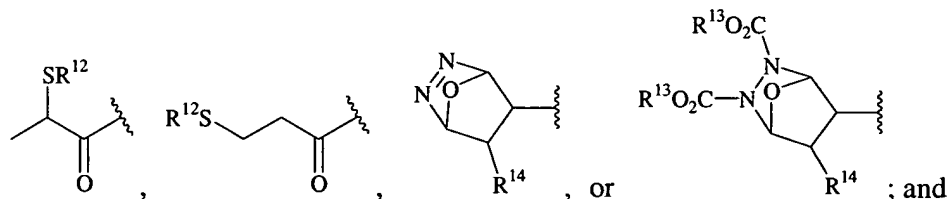


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or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, in which R^{22} is a leaving group or



R^{23} is



W is SR^7 , OR^7 or NHR^7 ;

wherein R^4 and R^6 are independently hydrogen, hydroxy, halogen, C_{1-4} alkyl,

C_{1-4} alkoxy, C_{1-4} alkylamino, C_{1-4} alkyldiamino, C_{1-4} alkylthio,

C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbamoyl,

dicarbamoyl, carbamyl, C_{1-4} alkoxy carbonyl, cyano, nitro, or trifluoromethyl;

R^5 is phenyl, pyridyl, furyl, thiazolyl, imidazolyl or thienyl, each optionally having one or two substituents that are independently halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, cyano, C_{1-6} alkyl-NH or $(C_{1-6} \text{ alkyl})_2N$;

Z is hydrogen, halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{3-8} cycloalkoxy,

nitro, C_{1-6} haloalkyl, hydroxy, C_{1-6} acyloxy, NH_2 , C_{1-6} alkyl-NH,

$(C_{1-6} \text{ alkyl})_2N$, C_{3-8} cycloalkyl-NH, $(C_{3-8} \text{ cycloalkyl})_2N$, hydroxymethyl,

C_{1-6} alkylcarbonyl, cyano, azido, C_{1-6} thioalkyl, C_{1-6} sulfinylalkyl,

C₁₋₆ sulfonylalkyl, C₃₋₈ thiocycloalkyl, C₃₋₈ sulfinylcycloalkyl, C₃₋₈ sulfonylcycloalkyl, mercapto, C₁₋₆ alkoxycarbonyl, C₃₋₈ cycloalkoxycarbonyl, C₂₋₄ alkenyl, C₄₋₈ cycloalkenyl, or C₂₋₄ alkynyl, provided that when Z is monovalent, R⁵ is absent;

R⁷ is hydrogen, C₁₋₆ alkyl, piperidin-1-yl-(CH₂)_m, piperazin-1-yl-(CH₂)_m, 4-C₁₋₆ alkyl-piperazin-1-yl-(CH₂)_m, pyrrolidin-1-yl-(CH₂)_m, pyridinyl-(CH₂)_m, imidazolyl-(CH₂)_m, imidazol-1-yl-(CH₂)_m, morpholin-4-yl-(CH₂)_m, thiomorpholin-4-yl-(CH₂)_m, or hexahydroazepin-1-yl-(CH₂)_m, wherein each C₁₋₆ alkyl optionally includes one or more substituents that are OH, NH₂ or -N(A)B;

R¹² is C₁₋₆ alkyl or aryl;

R¹³ is C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, TMS-(CH₂)_m or aryl-(CH₂)_m;

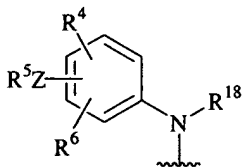
R¹⁴ is hydrogen, halogen, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and C₂₋₆ alkenyl or C₂₋₆ alkynyl substituted with hydroxy, alkoxy, amino or alkylamino;

R¹⁸ is hydrogen, an O-substituted carbonyldioxy radical, or an S-substituted sulfonyl radical, the O-substituted carbonyldioxy radical or the S-substituted sulfonyl radicals independently substituted with *t*-butyl, allyl, benzyl, *p*-methoxybenzyl, 2-chloroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-nitroethyl, 2-cyanoethyl, 4-nitrobenzyl, trifluoroacetyl or Tf;

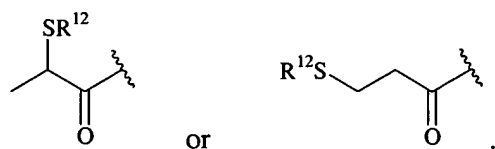
A and B are independently hydrogen, C₁₋₆ alkyl, (CH₂)_mOH, piperidin-1-yl-(CH₂)_m, piperazin-1-yl-(CH₂)_m, 4-C₁₋₆ alkyl-piperazin-1-yl-(CH₂)_m, pyrrolidin-1-yl-(CH₂)_m, pyridinyl-(CH₂)_m, imidazolyl-(CH₂)_m, or imidazol-1-yl-(CH₂)_m; and

m is an integer from zero to four, inclusive.

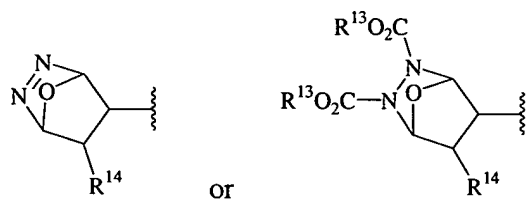
46. The compound of claim 44, wherein R²² is



47. The compound of claim 46, wherein R^{18} is hydrogen and R^{23} is

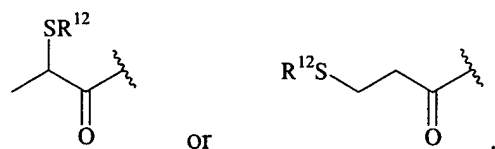


48. The compound of claim 46, wherein R^{18} is hydrogen and R^{23} is

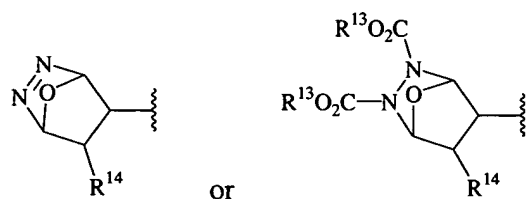


49. The compound of claim 44, wherein R^{22} is a leaving group.

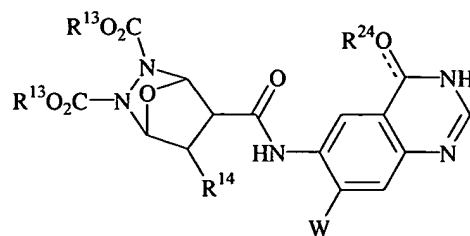
50. The compound of claim 49, wherein R^{18} is hydrogen and R^{23} is



51. The compound of claim 49, wherein R^{18} is hydrogen and R^{23} is



52. A compound of Formula 49,



or a pharmaceutically acceptable salt, ester, amide or prodrug thereof, in which

R^{13} is C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, $TMS-(CH_2)_m$ or aryl- $(CH_2)_m$;

R^{14} is hydrogen, halogen, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{2-6} alkenyl or C_{2-6} alkynyl substituted with hydroxy, alkoxy, amino or alkylamino;

R^{24} is $P^+(R^{16})_3$ or is absent;

W is SR^7 , $OR^{7'}$ or NHR^7 ;

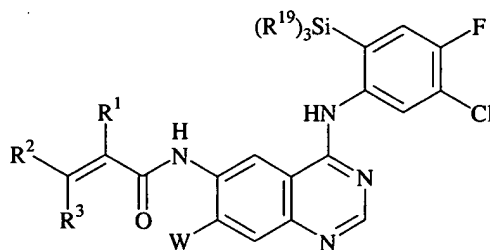
R^7 is hydrogen, C_{1-6} alkyl, piperidin-1-yl- $(CH_2)_m$, piperazin-1-yl- $(CH_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(CH_2)_m$, pyrrolidin-1-yl- $(CH_2)_m$, pyridinyl- $(CH_2)_m$, imidazolyl- $(CH_2)_m$, imidazol-1-yl- $(CH_2)_m$, morpholin-4-yl- $(CH_2)_m$, thiomorpholin-4-yl- $(CH_2)_m$, or hexahydroazepin-1-yl- $(CH_2)_m$, wherein each C_{1-6} alkyl optionally includes one or more substituents that are OH, NH_2 or -N(A)B;

R^{16} is C_{1-6} alkyl, phenyl, or phenoxy;

A and B are independently hydrogen, C_{1-6} alkyl, $(CH_2)_mOH$, piperidin-1-yl- $(CH_2)_m$, piperazin-1-yl- $(CH_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(CH_2)_m$, pyrrolidin-1-yl- $(CH_2)_m$, pyridinyl- $(CH_2)_m$, imidazolyl- $(CH_2)_m$, or imidazol-1-yl- $(CH_2)_m$;
and

m is an integer from zero to four, inclusive.

53. A compound of Formula 45,



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or a pharmaceutically acceptable salt, ester, amide or prodrug thereof, in which

R^1 , R^2 and R^3 are independently hydrogen, halogen, NO_2 , CN, CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} heterocyclyl, carboxy, C_{1-6} alkoxy carbonyl, C_{1-6} alkyl carbamoyl, aryl- $(CH_2)_m$, heteroaryl- $(CH_2)_m$, heterocyclyl- $(CH_2)_m$, $(CH_2)_mCO_2R^8$, $(CH_2)_mS(O)_nR^8$, $(CH_2)_mSO_2NR^8R^9$, OR^8 , SR^8 , $(CH_2)_mNR^8R^9$, $(CH_2)_mN(O)R^8R^9$,

$(\text{CH}_2)_m\text{P}(\text{O})(\text{OR}^8)(\text{OR}^9)$, $(\text{CH}_2)_m\text{COR}^8$, $(\text{CH}_2)_m\text{CO}_2\text{R}^8$, $(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{R}^9$,
 $(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{SO}_2\text{R}^8$, $(\text{CH}_2)_m\text{NR}^8\text{SO}_2\text{R}^9$, $(\text{CH}_2)_m\text{C}(\text{O})\text{NR}^8\text{OR}^9$,
 $(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^8$, or $(\text{CH}_2)_m\text{SO}_2\text{NR}^8\text{R}^9$, wherein aryl- $(\text{CH}_2)_m$ includes
 phenylalkyl or substituted phenylalkyl having from one to three substituents
 that are independently NO_2 , CN , CF_3 , C_{1-6} alkyl-NH, $(\text{C}_{1-6}$ alkyl) $_2\text{N}$, or
 monocyclic heteroaryl, and each C_{1-6} alkyl is optionally substituted with OH,
 NH_2 or $-\text{N}(\text{A})\text{B}$;

R^{19} is C_{1-4} alkyl, C_{1-4} alkoxy or aryl;

W is SR^7 , OR^7 or NHR^7 ; and

wherein, R^7 is hydrogen, C_{1-6} alkyl, piperidin-1-yl- $(\text{CH}_2)_m$, piperazin-1-yl- $(\text{CH}_2)_m$, 4-
 C_{1-6} alkyl-piperazin-1-yl- $(\text{CH}_2)_m$, pyrrolidin-1-yl- $(\text{CH}_2)_m$, pyridinyl- $(\text{CH}_2)_m$,
 imidazolyl- $(\text{CH}_2)_m$, imidazol-1-yl- $(\text{CH}_2)_m$, morpholin-4-yl- $(\text{CH}_2)_m$,
 thiomorpholin-4-yl- $(\text{CH}_2)_m$, or hexahydroazepin-1-yl- $(\text{CH}_2)_m$, wherein each
 C_{1-6} alkyl optionally includes one or more substituents that are OH, NH_2 or
 $-\text{N}(\text{A})\text{B}$;

R^8 and R^9 are each independently hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl,
 C_{2-6} alkynyl, arylalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or
 heteroarylalkyl;

A and B are independently hydrogen, C_{1-6} alkyl, $(\text{CH}_2)_m\text{OH}$, piperidin-1-yl- $(\text{CH}_2)_m$,
 piperazin-1-yl- $(\text{CH}_2)_m$, 4- C_{1-6} alkyl-piperazin-1-yl- $(\text{CH}_2)_m$, pyrrolidin-1-
 yl- $(\text{CH}_2)_m$, pyridinyl- $(\text{CH}_2)_m$, imidazolyl- $(\text{CH}_2)_m$, or imidazol-1-yl- $(\text{CH}_2)_m$;
 and

n and m are, respectively, integers from zero to two, inclusive, and from zero to four,
 inclusive.

54. The compound of claim 53, wherein R^1 , R^2 and R^3 are each hydrogen.

55. The compound of claim 53, wherein W is morpholin-4-yl-alkoxy.